Novel Gelators of Bile Acid–Alkylamine Salt Prepared through a Combinatorial Library Approach

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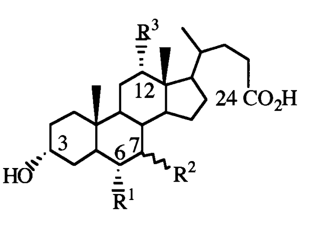
A combinatorial library approach enables us to find new low molecular-weight organogelators composed of a bile acid –alkylamine salt; the gel phenomena are investigated by FT-IR spectroscopy, SEM, and X-ray crystallography.

Particular attention is paid to the search of low molecular-weight organogelators, which are known as molecules capable of hardening some organic liquids.[1] Many studies have revealed the mechanism of the physical gelation; these molecules form intertwining fibrous aggregates in an organic solution via intermolecular interactions, such as hydrogen-bonding, electrostatic interaction, π–π interaction, and metal ligand interaction.[1–10] Moreover, important features or development of gelling agents have been reported.[2] In spite of these studies, a question as to what is required for the molecular structure for gel-forming has not been answered due to complexity and lack of directionality of the intermolecular forces.

A combinatorial library approach, which has been widely used for screening drugs and biological receptors, is expected to be useful in finding new gelators. In particular, use of organic acid–amine salts has advantages for screening the functional materials for several reasons; many salts can be easily prepared by mixing commercially available acids and amines; they are expected to form the aggregates by strong intermolecular interactions, such as hydrogen bonds and electrostatic interactions. In practice search for synthetic nanoporous materials[11] and selective reactions[12] have been reported. Moreover, it has been recently reported that ammonium carboxylates have gelation ability.[10] Here, we report novel gelators composed of acid and amine prepared by the combinatorial library approach, and a plausible mechanism for the gelation. Bile acids and alkylamines, having long alkyl chains, were used because many gelators have steroidal[3–6] and/or long alkyl chain units.[1,6–10]



	R^1	R^2	R^3
1	H	α-OH	OH
2	OH	α-OH	H
3	OH	H	H
4	H	α-OH	H
5	H	β-OH	H
6	H	H	OH
7	H	H	H

$CH_3(CH_2)_nNH_2$ n = 17 : **a** 13 : **d** 7 : **g**
16 : **b** 11 : **e** 5 : **h**
15 : **c** 9 : **f** 3 : **i**

$CH_3(CH_2)_7CH{=}CH(CH_2)_8NH_2$ **j**

$CH_3(CH_2)_{17}NR^1R^2$ R^1=H R^2=CH_3 **k**
R^1=CH_3 R^2=CH_3 **l**

Commercially available seven bile acids **1**–**7** and twelve alkylamines **a**–**l** were used as acidic and basic components, respectively. Mixing equimolar amounts of an acid and an alkylamine yielded a solid salt. A part of the results of the gelation tests is shown in Table 1 with the minimum gel concentration in parenthesis.[13] A salt **3•a** causes physical gelation in a wide variety of organic solvents, while salts of other bile acids and alkylamine **a** (**1•a**, **2•a**, **4•a**, **5•a**, **6•a,** and **7•a**) and salts of bile acid **3** and secondary or tertiary amines (**3•k** and **3•l**) have poor gelation ability. The **3•a** gels, which were colorless and transparent in appearance, were so stable that they did not transform to crystals or viscoelastic fluids for months. The gelation of salts **3** and other primary amines was also confirmed; salts **3•b**–**3•f** form gels in acetophenone solution at a concentration range of 20–33 g·dm^{-3}, salts **3•b**–**3•f** in cotton seed oil at a concentration range of 20–100 g·dm^{-3}, and salts **3•b**–**3•e** and **3•j** in benzene solution at a concentration range of 5–50 g·dm^{-3}. In addition, the salt **7•j** can form gel with a wide variety of organic solvents at a concentration range of 3–100 g·dm^{-3}, while the salt **7•a** has no gel-forming ability.

Table 1. Gelation tests[a] of **1**-**7•a** and minimum gel concentrations (g·dm^{-3})

Solvent	1•a	2•a	3•a	4•a	5•a	6•a	7•a
Ethanol	S	S	S	S	C	C	S
2-Butanone	C	P	G(100)	P	C	C	C
Acetophenone	G(50)	P	G(25)	S	C	G(25)	C
Ethyl acetate	C	I	I	I	C	C	I
Methyl benzoate	G(50)	P	G(30)	P	C	G(100)	C
Diisopropyl ether	I	I	I	C	C	I	I
THF	C	S	S	S	C	C	C
Anisole	G(15)	P	G(1)	P	C	G(100)	C
Benzene	G(30)	P	G(2)	P	P	I	C
Toluene	G(30)	P	G(2)	P	P	I	C
Chloroform	C	G(100)	G(20)	S	S	S	C
Chlorobenzene	G(50)	P	G(2)	P	P	I	C
DMF	C	C	G(100)	C	C	C	C
DMSO	C	P	G(100)	G(30)	C	C	C
Cotton Seed Oil	I	S	G(50)	P	I	I	I

[a]G=gel, S=solution, C=crystal, I=insoluble, P=precipitation

The results of gelation test **1a**–**7a** and **3a**-3**l** suggest that both of intermolecular hydrogen-bonding and hydrophobic interactions play an important role in physical gelation. The hydrogen-bonding interactions of **3•a** gel were confirmed by FT-IR spectrum. The benzene gel formed by **3•a** (30 g·dm^{-3}) exhibited a clear absorption peak at 1484 cm^{-1} and a broad peak at 3291 cm^{-1}, which were assigned to alkylammonium carboxylates and hydrogen-bonded hydroxy groups, respectively.

The detailed hydrogen bond network of the **3•a** was presumed by the crystal structure of a 1:1 salt **3•g** that was analyzed by X-ray crystallography.[14] As shown in Figure 1, the crystal of the salt **3•g** has a bilayered structure composed of hydrophilic and lipophilic layers. The lipophilic layers are accumulated only by van der Waals forces. On the other hand, the hydrophilic layers are maintained by two types of hydrogen-bond networks; one is a ladder-like network of alkylammonium nitrogens and carboxylate oxygens (Figure 2(a)), the other is a helical network of hydroxy groups at 3 and 6 positions on the steroid (Figure 2(b)). Because the ladder-like network is observed in many salt crystals of carboxylic acids and primary amines,[15] the network may be constructed in gel state of the salt **3•a** as the main driving force.

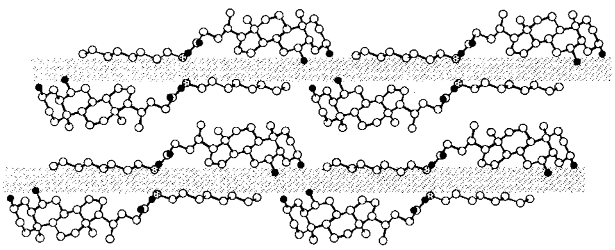


Figure 1. Packing diagram of a 1:1 salt of **3•g**. Empty, dotted, and closed circles represent carbon, nitrogen, and oxygen atoms, respectively. Hydrogen atoms are omitted for clarity. Shaded tapes represent hydrophilic layers.

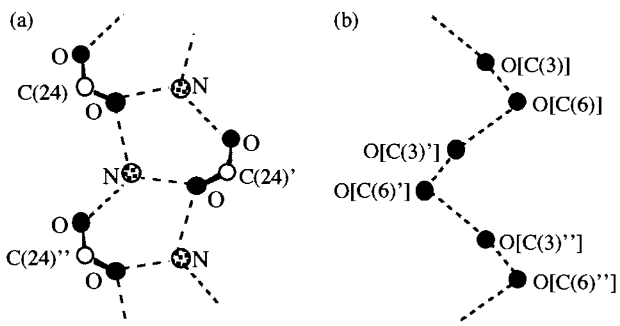


Figure 2. Schematic representation of hydrogen-bond networks in the crystal of **3•g**; (a) a ladder-like network of the alkylammo-nium carboxylate, (b) a helical network of hydroxy groups at 3 and 6 positions on the steroid. Hydrogen atoms are omitted for clarity. The atom coding is identical to that in Figure 1.

Figure 3 shows the SEM image of a xerogel that was obtained from the benzene gel of **3•a** by freeze-drying. The fibers observed had a cylindrical shape with ca. 2–7 μm diameter. This image reminds us of a plausible mechanism of ribbon windings described by Fuhrhop et al.[16] It seems that the cylinders are formed by twisted or rolled up thin sheets that are mainly retained by the ladder-like hydrogen bonds on the basis of the **3•g** crystal structure. The difference in the results of getting gel and crystal states for salts **3•a** and **3•g**, respectively, must be attributed to van der Waals interaction. Flexibility of a long alkyl chain of **3•a** molecule would make it difficult to stack among the lipophilic layers. This assumption is supported by the results of the gelation tests; the salts having a longer alkyl chain (**3•a–f**, and **3•j**) can form gel, but not the salts having a shorter alkyl chain (**3•g–i**).

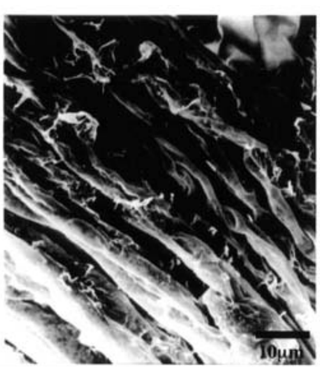


Figure 3. Scanning electron micrograph of a xerogel from salt **3•a** in benzene.

In conclusion, we demonstrate that the combinatorial library approach is useful in finding new two-componet type of gelling agent.[17] Some salts of bile acids and alkylamines can cause physical gelation in a wide variety of organic solvents. The plausible mechanism for the gelation with forming the fibrous aggregates was proposed based on the SEM image and on the crystal structure of an analogue. Preparation of novel gelators composed of other acid and amine salts are now in progress based on the combinatorial library approach.

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13 A typical procedure for gelation is as follows: A weighed salt was placed in a screw-capped test tube containing an organic liquid (5.0 mL) and the solvent was heated until the solid dissolved. The resulting solution was cooled at room temperature for 5 h and then the gelation was checked visually. The test tube filled with gelled sample could be turned upside down without causing significant flow.
14 Crystal structure data for **3•g** : $C_{32}H_{59}O_5N$, monoclinic, space group $P2_1$, a = 10.37(2), b = 6.323(1), c = 24.079(7)Å, b = 100.409(4)°, V = 1552(1) Å^3, D_{calc} = 1.116 g cm^{-3}, Z = 2, μ(Mo Kα) = 0.71 cm^{-1}, 2521 independent reflections (2θ max = 50.3°), R = 0.043.
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